09/441,966 SEARCH RESULTS/HISTORY

(FILE 'HOME' ENTERED AT 17:36:42 ON 25 JUN 2002)

FILE 'MEDLINE, AGRICOLA, CAPLUS, BIOSIS, EMBASE, WPIDS' ENTERED AT
17:39:34 ON 25 JUN 2002

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L1            2 S BIKUNIN AND ((CYSTIC (W) FIBROSIS) OR MUCUS OR SPUTUM OR ASTH
L2           29 S KUNITZ AND ((CYSTIC (W) FIBROSIS) OR MUCUS OR SPUTUM OR ASTHM
L3           16 DUP REM L2 (13 DUPLICATES REMOVED)
L4          168 S APROTININ AND ((CYSTIC (W) FIBROSIS) OR MUCUS OR SPUTUM OR AS
L5          121 DUP REM L4 (47 DUPLICATES REMOVED)
L6           99 S L5 NOT PY>1998
L7           13 S L6 AND APROTININ/TI
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=>

TINUE? Y/(N):y

L1 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:441647 CAPLUS
DOCUMENT NUMBER: 133:84295
TITLE: Kunitz-type serine proteinase inhibitors for accelerating the rate of **mucociliary** clearance
INVENTOR(S): Hall, Roderick; Poll, Christopher T.; Newton, Benjamin B.; Taylor, William J. A.
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037099	A2	20000629	WO 1999-GB4381	19991222
WO 2000037099	A3	20001026		
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1140150	A2	20011010	EP 1999-963636	19991222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-218913 A 19981222
US 1999-441966 A 19991117
WO 1999-GB4381 W 19991222

AB The instant invention provides for a compn. and method for using Kunitz-type serine protease inhibitors, e.g., aprotinin or **bikunin**, for stimulating the rate of **mucociliary** clearance of **mucus** and **sputum** in lung airways of subjects afflicted with **mucociliary** dysfunctions such as **cystic fibrosis**.

L1 ANSWER 2 OF 2 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-452127 [39] WPIDS
DOC. NO. CPI: C2000-137761
TITLE: Stimulating **mucociliary** clearance rate of **mucus** and **sputum** in lung airways for treating lung diseases such as **cystic fibrosis** and **bronchitis** involves administering a Kunitz-type serine protease inhibitor.
DERWENT CLASS: B04 D16
INVENTOR(S): HALL, R; NEWTON, B B; POLL, C T; TAYLOR, W J A
PATENT ASSIGNEE(S): (FARB) BAYER AG
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000037099	A2	20000629	(200039)*	EN	173
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN ZA ZW					
AU 2000019878	A	20000712	(200048)		
EP 1140150	A2	20011010	(200167)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
CN 1334743	A	20020206	(200231)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000037099	A2	WO 1999-GB4381	19991222

09/816,860 SEARCH RESULTS/HISTORY

AU 2000019878	A	AU 2000-19878	19991222
EP 1140150	A2	EP 1999-963636	19991222
		WO 1999-GB4381	19991222
CN 1334743	A	CN 1999-816145	19991222

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000019878	A	Based on	WO 200037099
EP 1140150	A2	Based on	WO 200037099

PRIORITY APPLN. INFO: US 1999-441966 19991117; US 1998-218913 19981222

AN 2000-452127 [39] WPIDS

AB WO 200037099 A UPAB: 20000818

NOVELTY - Accelerating the rate of **mucociliary** clearance in a subject comprising administering a composition (I) comprising a Kunitz-type serine protease inhibitor (KSPI).

ACTIVITY - Antiinflammatory. The effect of the Kunitz family serine protease inhibitor, **bikunin**, was studied on sheep tracheal **mucus** velocity (TMV) over 8 hours after treatment with **bikunin**. 9 mg **bikunin** (3 ml of 3 mg/ml) was administrated by a nebulized aerosol to the airways and to measure TMV, 5-10 radiopaque Teflon (RTM) particles were insufflated into the trachea via a catheter placed within the endotracheal tube. The movement of the Teflon (RTM) particles was then measured for 1 minute. TMV was calculated from the average distance in a cephalad direction traveled per minute for 5 - 10 Teflon particles. Baseline TMV was measured immediately prior to administration of the aerosol for 8 hours with an interval of 1 hour. The results showed that **bikunin** aerosol delivered to sheep airways significantly increased TMV at 8 hours compared to the same time for a group of animals receiving phosphate buffered saline (PBS) vehicle aerosol.

MECHANISM OF ACTION - Serine protease inhibitor.

USE - Kunitz-type serine protease inhibitors are useful for stimulating the rate of **mucociliary** clearance of **mucus** and **sputum** in the lung airways (claimed). The inhibitors are useful for treating lung diseases such as **cystic fibrosis**, chronic **bronchitis**, **bronchiectasis** and chronic **sinusitis** and glue ear caused by retention and accumulation of **mucus**.

ADVANTAGE - The composition reduces or eliminates **mucus** and **sputum** in lung airways in patients with chronic obstructive lung disease and reduces the risk of secondary lung infections and other adverse side effects, as well as avoiding or delaying the need for lung transplant surgery in **cystic fibrosis** patients. Inhibitors are human proteins and therefore reduce the risk of kidney damage on administration of large doses of Trasylol proteins.

Dwg.0/31

=> d his

(FILE 'HOME' ENTERED AT 17:36:42 ON 25 JUN 2002)

FILE 'MEDLINE, AGRICOLA, CAPLUS, BIOSIS, EMBASE, WPIDS' ENTERED AT 17:39:34 ON 25 JUN 2002

L1 2 S BIKUNIN AND ((CYSTIC (W) FIBROSIS) OR MUCUS OR SPUTUM OR ASTH

=> s kunitz and ((cystic (w) fibrosis) or mucus or sputum or asthma or mucociliary or bronchitis or bronchiectasis or sinusitis)

L2 29 KUNITZ AND ((CYSTIC (W) FIBROSIS) OR MUCUS OR SPUTUM OR ASTHMA OR MUCOCILIARY OR BRONCHITIS OR BRONCHIECTASIS OR SINUSITIS)

=> dup rem l2

PROCESSING COMPLETED FOR L2

L3 16 DUP REM L2 (13 DUPLICATES REMOVED)

=> d 1- ibib abs

YOU HAVE REQUESTED DATA FROM 16 ANSWERS - CONTINUE? Y/(N):y

L3 ANSWER 1 OF 16 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2002172859 MEDLINE

DOCUMENT NUMBER: 21855766 PubMed ID: 11867337

TITLE: Protection against acute lung injury by intravenous or intratracheal pretreatment with EPI-HNE-4, a new potent neutrophil elastase inhibitor.

COMMENT: Comment in: Am J Respir Cell Mol Biol. 2002 Mar;26(3):266-8
AUTHOR: Delacourt Christophe; Herigault Sabine; Delclaux Christophe; Poncin Alain; Levame Micheline; Harf Alain; Saudubray Francois; Lafuma Chantal
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Scientifique, Faculte de Medecine, Creteil, France.
SOURCE: AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, (2002 Mar) 26 (3) 290-7.
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020322
Last Updated on STN: 20020403
Entered Medline: 20020329

AB Excessive accumulation of active neutrophil elastase (NE) in pulmonary fluids and tissues of patients with **cystic fibrosis** (CF) is thought to act on the lungs, compromising their structure and function. The aim of this study was to investigate the in vitro and in vivo protective effect of a new, rapidly acting, potent (Ki = 5.45 x 10(-12) M and Kon = 8 x 10(6) M(-1) s(-1)) and specific human NE inhibitor, EPI-HNE-4, engineered from the **Kunitz** domain. The results demonstrated that this inhibitor was able to (i) effectively inhibit in vitro the high levels of active NE present in a medium as complex as **sputum** from children with CF, with a measured IC(50) equal or close to the calculated IC(50) in 60% of cases, and (ii) almost completely block (91%) the N-formyl-methionine-leucine-phenylalanine-induced migration of purified human neutrophils across a Matrigel basement membrane. Intratracheal administration (250, 175, or 100 microg per rat) of the inhibitor 5 min before instillation of pure human NE (HNE) (150 microg per rat) to rats induced effective, dose-dependent protection of the lungs, 4 h later, from hemorrhage, serum albumin leakage, residual active NE, and discrete neutrophil influx in air spaces induced by instillation of pure HNE. Intravenous administration (3 mg per rat) of EPI-HNE-4, 15 min before instillation of the soluble fraction of pooled **sputum** (delivering 120 microg of active NE per rat) from children with CF, effectively reduced (64%), 4 h later, the massive neutrophil influx induced by **sputum** instillation. Overall, these data strongly suggest that associated aerosol and systemic administration of EPI-HNE-4 would be beneficial in the treatment of CF.

L3 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
ACCESSION NUMBER: 2001:703054 CAPLUS
DOCUMENT NUMBER: 135:267267
TITLE: Protein and cDNA sequences of a novel human protein BTL.009 having proteinase inhibitor activity
INVENTOR(S): Delaria, Kathy; Roczniak, Steve; Davies, Christopher
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S., 16 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6294648	B1	20010925	US 1999-358569	19990720

AB The invention provides protein and cDNA sequences of a novel human protein BTL.009, which is a novel human serine proteinase inhibitor of the **Kunitz** family that exhibits greater potency towards neutral serine proteinases, particularly leukocyte elastase, and chymotrypsin than towards trypsin-like proteinases. BTL.009 has been identified as a member of the **Kunitz** family of proteinase inhibitors based on the presences of the conserved six cysteines obsd. in all members of this family. BTL.009, or variants thereof, may be employed as therapeutics in diseases such as emphysema, idiopathic pulmonary fibrosis, adult respiratory distress syndrome, **cystic fibrosis**, rheumatoid arthritis, organ failure, and glomerulonephritis in which uncontrolled proteolysis due to neutral serine proteinase activity results in tissue damage.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 2001:75295 CAPLUS

09/816,860 SEARCH RESULTS/HISTORY

DOCUMENT NUMBER: 134:141769
TITLE: Protein having proteinase inhibitor activity
INVENTOR(S): Davies, Christopher; Chen, Dadong; Roczniak, Steve
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 17 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6180607	B1	20010130	US 1999-369494	19990805

AB BTL.010 is a novel human serine proteinase inhibitor of the **Kunitz** family that exhibits greater potency towards neutral serine proteinases, particularly leukocyte elastase-, and proteinase 3, than towards trypsin-like proteinases. BTL.010, or variants thereof, may be employed as therapeutics in diseases such as emphysema, idiopathic pulmonary fibrosis, adult respiratory distress syndrome, **cystic fibrosis**, rheumatoid arthritis, organ failure, and glomerulonephritis in which uncontrolled proteolysis due to neutral serine proteinase activity results in tissue damage.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 16 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-147325 [15] WPIDS
DOC. NO. CPI: C2001-043631
TITLE: Recombinant protein derived from ticks that is capable of inhibiting human mast cell tryptase activity, useful for treating and preventing inflammation in humans or animals, and for the depletion or removal of tryptase from a food product.
DERWENT CLASS: B04 D16
INVENTOR(S): NUTTALL, P A; PAESEN, G C
PATENT ASSIGNEE(S): (EVOL-N) EVOLUTEC LTD
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001005823	A2	20010125	(200115)*	EN	32

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000060040	A	20010205	(200128)	
BR 2000012589	A	20020409	(200232)	
EP 1196579	A2	20020417	(200233)	EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001005823	A2	WO 2000-GB2791	20000719
AU 2000060040	A	AU 2000-60040	20000719
BR 2000012589	A	BR 2000-12589	20000719
		WO 2000-GB2791	20000719
EP 1196579	A2	EP 2000-946166	20000719
		WO 2000-GB2791	20000719

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000060040	A	Based on	WO 200105823
BR 2000012589	A	Based on	WO 200105823
EP 1196579	A2	Based on	WO 200105823

PRIORITY APPLN. INFO: GB 1999-16913 19990719
AN 2001-147325 [15] WPIDS
AB WO 200105823 A UPAB: 20010317
NOVELTY - A recombinant protein (I), its active fragment or functional

equivalent, derived from a blood-feeding arthropod ectoparasite, preferably ticks, that is capable of inhibiting the activity of a human mast cell tryptase, is new.

DETAILED DESCRIPTION - A recombinant protein (I), its active fragment or functional equivalent, derived from a blood-feeding arthropod ectoparasite, preferably ticks, that is capable of inhibiting the activity of a human mast cell tryptase, is new.

(I) exhibits significant sequence homology with the tick-derived protease inhibitor protein (TdPI; a 118 amino acid sequence (S1) as defined in the specification), its active fragment or its functional equivalent.

INDEPENDENT CLAIMS are also included for the following:

(1) a vaccine composition (VC) comprising (I)

(2) formulating VC, by bringing (I), its fragment or functional equivalent into association with a pharmaceutically acceptable carrier;

(3) a nucleic acid molecule (II) encoding (I);

(4) a nucleic acid molecule (IIa) having the 490 nucleotide sequence defined in the specification which hybridizes with (II) under stringent hybridization conditions, or which encodes (I);

(5) a viral vector (III) comprising (II) or (IIa);

(6) a host cell (IV) transformed or transfected with (III);

(7) a transgenic animal (V) transformed by (II) or (IIa);

(8) preparing (I) by culturing (IV); and

(9) a method for vaccinating a mammal against a disease, or for treating a mammal suffering from a disease, comprising administering (I), its fragment or functional equivalent.

ACTIVITY - Antiinflammatory; antiasthmatic; antipsoriatic; antirheumatoid; antiarthritic; antiallergic; cytostatic.

MECHANISM OF ACTION - Inhibitor of tryptase, preferably human mast cell tryptase; vaccine (claimed); gene therapy.

No supporting biological data given.

USE - (I) is useful as a pharmaceutical and in the manufacture of a medicament for treating inflammation in humans and animals. (I) is useful for treating and preventing inflammation in humans or animals. One or more epitopes of (I) can be used in the development of vaccines that target proteins that exhibit significant sequence homology with TdPI. (I) is useful for vaccinating a mammal against a disease. Bovine colostrum trypsin inhibitor, rat tissue factor pathway inhibitor (TFPI-2), **Kunitz** domain of tick anticoagulant peptide TAP or the two domains in ornithodorin, are useful as a tryptase inhibitor.

(I) is useful in the detection or quantification of tryptase, for the depletion or removal of tryptase from a food product or from a cell culture, as an anti-tryptase agent or as an antiinflammatory drug (all claimed).

(I) is useful for treating **asthma**, psoriasis, interstitial lung disease, rheumatoid arthritis, gingivitis, peridontitis, allergic reactions, cancer and any other tryptase-mediated condition. (I) is useful as an immunogen, and as a tool in the study of inflammation, inflammation-related processes, or other physiological processes involving tryptase. VC is useful for vaccinating against a broad range of arthropod and/or helminth genera.

Dwg.0/6

L3 ANSWER 5 OF 16 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2001336099 MEDLINE
DOCUMENT NUMBER: 21296832 PubMed ID: 11404240
TITLE: Na+ transport in normal and CF human bronchial epithelial cells is inhibited by BAY 39-9437.
COMMENT: Comment in: Am J Physiol Lung Cell Mol Physiol. 2001 Jul;281(1):L13-5
AUTHOR: Bridges R J; Newton B B; Pilewski J M; Devor D C; Poll C T; Hall R L
CORPORATE SOURCE: Department of Cell Biology and Physiology, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, USA.. bbridges+@pitt.edu
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. LUNG CELLULAR AND MOLECULAR PHYSIOLOGY, (2001 Jul) 281 (1) L16-23. Journal code: 100901229. ISSN: 1040-0605.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB To test the hypothesis that Na+ transport in human bronchial epithelial (HBE) cells is regulated by a protease-mediated mechanism, we investigated

the effects of BAY 39-9437, a recombinant **Kunitz**-type serine protease inhibitor, on amiloride-sensitive short-circuit current of normal [non-**cystic fibrosis** (CF) cells] and CF HBE cells. Mucosal treatment of non-CF and CF HBE cells with BAY 39-9437 decreased the short-circuit current, with a half-life of approximately 45 min. At 90 min, BAY 39-9437 (470 nM) reduced Na+ transport by approximately 70%. The inhibitory effect of BAY 39-9437 was concentration dependent, with a half-maximal inhibitory concentration of approximately 25 nM. Na+ transport was restored to control levels, with a half-life of approximately 15 min, on washout of BAY 39-9437. In addition, trypsin (1 microM) rapidly reversed the inhibitory effect of BAY 39-9437. These data indicate that Na+ transport in HBE cells is activated by a BAY 39-9437-inhibitable, endogenously expressed serine protease. BAY 39-9437 inhibition of this serine protease maybe of therapeutic potential for the treatment of Na+ hyperabsorption in CF.

L3 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
ACCESSION NUMBER: 2000:441647 CAPLUS
DOCUMENT NUMBER: 133:84295
TITLE: **Kunitz**-type serine proteinase inhibitors for accelerating the rate of **mucociliary** clearance
INVENTOR(S): Hall, Roderick; Poll, Christopher T.; Newton, Benjamin B.; Taylor, William J. A.
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037099	A2	20000629	WO 1999-GB4381	19991222
WO 2000037099	A3	20001026		
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1140150	A2	20011010	EP 1999-963636	19991222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-218913 A 19981222
US 1999-441966 A 19991117
WO 1999-GB4381 W 19991222

AB The instant invention provides for a compn. and method for using **Kunitz**-type serine protease inhibitors, e.g., aprotinin or bikunin, for stimulating the rate of **mucociliary** clearance of **mucus** and **sputum** in lung airways of subjects afflicted with **mucociliary** dysfunctions such as **cystic fibrosis**.

L3 ANSWER 7 OF 16 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1996-321851 [32] WPIDS
CROSS REFERENCE: 1990-115996 [15]; 1992-150877 [18]; 1992-331666 [40]; 1992-331723 [40]; 1992-331725 [40]
DOC. NO. CPI: C1996-102546
TITLE: New engineered inhibitors of human neutrophil elastase - contg. aprotinin-like **Kunitz** domain for treating, e.g. **cystic fibrosis** or other respiratory disorders.
DERWENT CLASS: B04 D16
INVENTOR(S): GUTERMAN, S; KENT, R; LADNER, R C; LEY, A C; MARKLAND, W; ROBERTS, B; GUTERMAN, S K; KENT, R B; ROBERTS, B L
PATENT ASSIGNEE(S): (DYAX-N) DYAX CORP; (PROT-N) PROTEIN ENG CORP
COUNTRY COUNT: 20
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9620278	A2	19960704	(199632)*	EN	106
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					

W: CA JP US
US 5663143 A 19970902 (199741) 147
EP 797666 A1 19971001 (199744) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 10510996 W 19981027 (199902) 116

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9620278	A2		WO 1995-US16349	19951215
US 5663143	A	CIP of	US 1988-240160	19880902
		CIP of	US 1990-487063	19900302
		Div ex	US 1991-664989	19910301
		CIP of	US 1993-9319	19930126
		CIP of	US 1993-133031	19931013
			US 1994-358160	19941216
EP 797666	A1		EP 1995-943819	19951215
			WO 1995-US16349	19951215
JP 10510996	W		WO 1995-US16349	19951215
			JP 1996-520491	19951215

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5663143	A	Div ex	US 5223409
		CIP of	US 5403484
EP 797666	A1	Based on	WO 9620278
JP 10510996	W	Based on	WO 9620278

PRIORITY APPLN. INFO: US 1994-358160 19941216; US 1988-240160 19880902; US 1990-487063 19900302; US 1991-664989 19910301; US 1993-9319 19930126; US 1993-133031 19931013

AN 1996-321851 [32] WPIDS

CR 1990-115996 [15]; 1992-150877 [18]; 1992-331666 [40]; 1992-331723 [40]; 1992-331725 [40]

AB WO 9620278 A UPAB: 19971013
Non-natural protein (I) comprises an engineered aprotinin-like **Kunitz** domain and inhibits human neutrophil elastase (hNE) with Ki < 50 pM. The domain has an amino acid (aa) sequence at least substantially homologous, over a region extending from first to last Cys, with one of the reference sequences EPI-HNE-3 or -4; DPI.1.1, 1.2, 1.3, 2.1, 2.2, 2.3, 3.1, 3.2, 3.3, 4.1, 4.2, 4.3, 5.1,5.2, 5.3, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 7.1, 7.2, 7.3, 7.4, 7.5, 8.1, 8.2, 8.3, 9.1, 9.2 or 9.3, but is not identical to any domain selected from EpiNE- alpha , EpiNE1-8, ITI-E7, BITI-E7-1222 , BITI-E7-141, AMINO 1 or 2, MUTP1, MUTT26A, MUTQE or MUT1619. Also new are (1) DNA (II) encoding (I); (2) expression vectors contg. (I) operably linked to regulatory sequences; (3) transformed cells contg. such vectors. The specification includes the sequences of the reference domains.
USE - (I) are inhibitors of hNE so are used to treat hereditary deficiency of circulating alpha -1-protease inhibitor (API), smoker's emphysema, destruction of lung tissue caused by excessive hNE activity, **cystic fibrosis** and other respiratory diseases.
ADVANTAGE - Unlike API, (I) are small, stable and non-toxic inhibitors of hNE.
Dwg.0/0

ABEQ US 5663143 A UPAB: 19971013
A protein that binds and inhibits human neutrophil elastase with a Ki less than about 10 picomolar comprising an amino acid sequence picked from the set of sequences EpiNE1, EpiNE2, EpiNE3, EpiNE4, EpiNE5, EpiNE6, EpiNE7, EpiNE8, EPI-HNE-2, EPI-HNE-3, EPI-HNE-4, BITI-E7, BITI-E7-141, BITI-E7-1222, MUT1619, MUTP1, AMINO1, AMINO2, MUTQE, MUTT26A, EpiNE7.6, EpiNE7.8, EpiNE7.9, EpiNE7.31, EpiNE 7.11, EpiNE7.7, EpiNE7.4, EpiNE7.14, EpiNE7.5, EpiNE7.10, EpiNE7.20, EpiNE7.1, EpiNE7.16, EpiNE7.19, EpiNE7.12, EpiNE7.17, EpiNE7.21, EpiNE7.22, EpiNE7.23, EpiNE7.24, EpiNE7.25, EpiNE7.26, EpiNE7.27, EpiNE7.28, EpiNE7.29, EpiNE7.30, EpiNE7.32, EpiNE7.33, EpiNE7.36, EpiNE7.37, EpiNE7.38, EpiNE7.39, and EpiNE7.40.
Dwg.0/0

L3 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:466606 CAPLUS
DOCUMENT NUMBER: 119:66606
TITLE: Manufacture of **Kunitz** proteinase inhibitor domain of amyloid precursor protein (APP) for therapeutic use and for modelling of APP processing

and amyloidosis
INVENTOR(S): Wagner, Steven L.; Siegel, Robert; Thill, Gregory P.; Harpold, Michael M.; Comer, William T.
PATENT ASSIGNEE(S): Salk Institute Biotechnology/Industrial Associates, Inc., USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9309233	A2	19930513	WO 1992-US9400	19921030
WO 9309233	A3	19930805		
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9230610	A1	19930607	AU 1992-30610	19921030

PRIORITY APPLN. INFO.: US 1991-785638 19911031
WO 1992-US9400 19921030

AB The **Kunitz** proteinase inhibitor (KPI) domain of the amyloid precursor protein is manufd. in yeast cells for use in the treatment of diseases such as Alzheimer's disease, coagulation disorders, and emphysema. An in vitro model of APP processing and disease origination involving addn. of the KPI to cultured neuronal cells is described. A synthetic gene encoding residues 285-345 of APP fused to the yeast .alpha.-mating factor signal sequence was expressed from the AOX1 promoter in Pichia pastoris. The KPI produced was purified and partially sequenced, its amino acid compn. detd., and its protease inhibitory activity examd. The in vitro model was demonstrated.

L3 ANSWER 9 OF 16 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1992-331666 [40] WPIDS
CROSS REFERENCE: 1990-115996 [15]; 1992-150877 [18]; 1992-331723 [40]; 1992-331725 [40]; 1996-321851 [32]
DOC. NO. CPI: C1992-147465
TITLE: New peptide inhibitors of elastase or cathepsin G - are e.g. mutants of **Kunitz** Domain serine protease inhibitors, useful for treating and preventing conditions caused by excessive neutrophil elastase or cathepsin G.
DERWENT CLASS: B04 D16 D21
INVENTOR(S): GUTERMAN, S K; KENT, R B; LADNER, R C; LEY, A C; MARKLAND, W; ROBERTS, B L; KENT, R
PATENT ASSIGNEE(S): (PROT-N) PROTEIN ENG CORP; (DYAX-N) DYAX CORP
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9215605	A2	19920917	(199240)*	EN	126
RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE					
W: AU CA FI JP NO US					
AU 9215816	A	19921006	(199301)		
EP 573603	A1	19931215	(199350)	EN	
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL SE					
JP 06510522	W	19941124	(199506)		
WO 9215605	A3	19921223	(199511)		
ES 2124203	T1	19990201	(199911)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9215605	A2	WO 1992-US1501	19920228
AU 9215816	A	AU 1992-15816	19920228
		WO 1992-US1501	19920228
EP 573603	A1	EP 1992-908481	19920228
		WO 1992-US1501	19920228
JP 06510522	W	JP 1992-508204	19920228
		WO 1992-US1501	19920228
ES 2124203	T1	EP 1992-908481	19920228

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 9215816	A	Based on	WO 9215605
EP 573603	A1	Based on	WO 9215605
JP 06510522	W	Based on	WO 9215605
ES 2124203	T1	Based on	EP 573603

PRIORITY APPLN. INFO: US 1991-715834 19910617; US 1991-664989 19910301
AN 1992-331666 [40] WPIDS
CR 1990-115996 [15]; 1992-150877 [18]; 1992-331723 [40]; 1992-331725 [40]; 1996-321851 [32]
AB WO 9215605 A UPAB: 19971013
An inhibitor of human neutrophil elastase (hNE) selected from EpiNEalpha, EpiNE1, EpiNE2, EpiNE3, EpiNE4, EpiNE5, EpiNE6, EpiNE7, EpiNE8, ITI-E7, BITI-E7, BITI-E7,-1222, AMINO1, AMINO2, MUTP1, BITI-E7-141, MUTT26A, MUTQE AND MUT1619 is new.

Also claimed are an inhibit or of human cathepsin Ci (hcG) selected from EpiC1, EpiC7, EpiC8, EpiC10, EpiC20, EpiC31, EpiC32, EpiC33, EpiC34 and EpiC35; a homologous inhibitor of a reference inhibitor as above but differing by one or more specific aminoacid substits.

USE - The inhibitors have high specific binding activity for hNE and/or hcG and can be used for the treatment or prophylaxis of condition caused by excessive hNE and/or hcG activity, e.g., inflammation, emphysema, **cystic fibrosis**, adult respiratory distress syndrome or rheumatoid arthritis. The proteins can also be used to purify the enzy

Dwg.0/18

L3 ANSWER 10 OF 16 MEDLINE
ACCESSION NUMBER: 82093827 MEDLINE
DOCUMENT NUMBER: 82093827 PubMed ID: 6172220
TITLE: Protease binding by alpha 2 macroglobulin in **cystic fibrosis**.
AUTHOR: Bridges M A; Applegarth D A; Johannson J; Wong L T; Davidson A G
SOURCE: CLINICA CHIMICA ACTA, (1982 Jan 5) 118 (1) 33-43. Journal code: 1302422. ISSN: 0009-8981.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198203
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19970203
Entered Medline: 19820322
AB The interaction of alpha 2 macroglobulin (alpha 2M) with exogenous proteases has been reported by others to be abnormal in **cystic fibrosis** (CF). We have re-examined these claims. Four parameters were considered:(1) the molar protease binding of alpha 2M; (2) the interaction of bovine cationic trypsin (BCT), complexed to alpha 2M, with low molecular mass substrate, benzoyl arginine ethyl ester (BAEE); (3) the stability of formed alpha 2 M-BCT complexes; and (4) the subunit structure of alpha 2M. We have found CF alpha 2M to be similar to control alpha 2M in every respect studied.

L3 ANSWER 11 OF 16 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 82074265 MEDLINE
DOCUMENT NUMBER: 82074265 PubMed ID: 6171497
TITLE: **Kunitz**-type proteinase inhibitors derived by limited proteolysis of the inter-alpha-trypsin inhibitor, V. Attachments of carbohydrates in the human urinary trypsin inhibitor isolated by affinity chromatography.
AUTHOR: Hochstrasser K; Schonberger O L; Rossmanith I; Wachter E
SOURCE: HOPPE-SEYLERS ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1981 Oct) 362 (10) 1357-62. Journal code: 2985060R. ISSN: 0018-4888.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198202
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19820212
AB The inhibitory active part of the inter-alpha-trypsin inhibitor with a known amino acid sequence is present as an acid-resistant inhibitor in human serum, in urine, in bronchial and in nasal **mucus**. The inhibitor molecule has a 50% carbohydrate content. Carbohydrate side

chains are attached in two positions. One chain is linked to the polypeptide O-glycosidically via the serine residue in position 10 in the N-terminal extension peptide. The second side chain is attached N-glycosidically via the asparagine residue in position 24, located in the inactive "inhibitory" **Kunitz**-type domain of the inhibitor. The composition of the carbohydrate side chains were determined.

L3 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1981:53133 BIOSIS
DOCUMENT NUMBER: BR20:53133
TITLE: THE ACID STABLE PROTEINASE INHIBITORS OF THE RESPIRATORY TRACT CHEMISTRY AND FUNCTION.
AUTHOR(S): HOCHSTRASSER K
CORPORATE SOURCE: KLINIK UND POLIKLINIK FUER HALS-, NASEN- UND OHRENKRANKE DER UNIVERSITAET MUENCHEN, KLINIKUM GROSSHADERN, POSTFACH 701 260, D-8000 MUENCHEN 70, FRG.
SOURCE: INTERNATIONAL SYMPOSIUM ON BIOCHEMISTRY, PATHOLOGY AND GENETICS OF PULMONARY EMPHYSEMA, PORTO CONTE, SASSARI, ITALY, APRIL 27-30, 1980. CLIN RESPIR PHYSIOL, (1980 (RECD 1981)) 16 (SUPPL), 223-230.
CODEN: CRPHD4. ISSN: 0272-7587.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L3 ANSWER 13 OF 16 MEDLINE
ACCESSION NUMBER: 77224156 MEDLINE
DOCUMENT NUMBER: 77224156 PubMed ID: 69510
TITLE: Abnormal breakdown of alpha2-macroglobulin-trypsin complex in **cystic fibrosis**.
AUTHOR: Shapira E; Ben-Yoseph Y; Nadler H L
SOURCE: CLINICA CHIMICA ACTA, (1977 Aug 1) 78 (3) 359-63.
Journal code: 1302422. ISSN: 0009-8981.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197709
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19770922
AB The complex of trypsin with purified alpha2-macroglobulin from normals and patients with **cystic fibrosis** was studied. The formed complex failed to reveal any proteolytic activity toward a high molecular weight substrate whereas the esterolytic activity towards a low molecular weight substrate was retained. This esterolytic activity was resistant to inhibition by a high molecular weight inhibitor. During iincubation at 38 degrees C the complex with normal alpha2-macroglobulin was slowly inhibited by the high molecular weight inhibitor and regained activity with the high molecular weight substrate. This phenomenon was not obtained when the alpha2-macroglobulin from **cystic fibrosis** was examined. These data suggest that the gradual conversion of normal alpha2-macroglobulin-trypsin complex into an alpha2-macroglobulin fragment-trypsin complex is deficient in patients with **cystic fibrosis**.

L3 ANSWER 14 OF 16 MEDLINE
ACCESSION NUMBER: 77089874 MEDLINE
DOCUMENT NUMBER: 77089874 PubMed ID: 832413
TITLE: Plasma arginine esterase activity in **cystic fibrosis** of the pancreas.
AUTHOR: Chan K Y; Applegarth D A; Davidson A G
SOURCE: CLINICA CHIMICA ACTA, (1977 Jan 3) 74 (1) 71-5.
Journal code: 1302422. ISSN: 0009-8981.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197703
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19970203
Entered Medline: 19770321
AB Using a micro-method for the determination of plasma arginine esterase activity, we have investigated the values for soybean trypsin inhibitor (STI)-inhibited arginine esterase activity in patients with **cystic fibrosis**, obligate heterozygotes and age matched control individuals. The mean of STI-inhibited activity is lowest for **cystic fibrosis** patients while the mean for normal controls is the highest. The mean of STI-inhibited activity for the

heterozygotes is midway between the values of the patients and the normal individuals. The deficiency of arginine esterase activity was statistically significant for both **cystic fibrosis** patients and heterozygotes.

L3 ANSWER 15 OF 16 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 76141310 MEDLINE
DOCUMENT NUMBER: 76141310 PubMed ID: 3462
TITLE: [The disulfide bridges of the trypsin-kallikrein inhibitor K from snails (Helix pomatia). Thermal inactivation and proteolysis by thermolysin (author's transl)].
Die Disulfidbrucken des Trypsin-Kallikrein-Inhibitors K aus Weinbergschnecken (Helix pomatia). Thermische Denaturierung und thermolysinolytische Inaktivierung.
AUTHOR: Dietl T; Tschesche H
SOURCE: HOPPE-SEYLERS ZEITSCHRIFT FUR PHYSIOLOGISCHE CHEMIE, (1976 Feb) 357 (2) 139-45.
Journal code: 2985060R. ISSN: 0018-4888.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197606
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19950206
Entered Medline: 19760602

AB Isoinhibitor K is the main component of the complex mixture of isoinhibitors of broad specificity secreted into the **mucus** by the Roman snail (Helix pomatia). The disulfide pairing was determined after the amino acid sequence had been elucidated. Two cystine-containing peptides with the disulfide bridges Cys32-Cys53 and Cys32-Cys53 plus Cys7-Cys57 were obtained after thermolytic hydrolysis of the native inhibitor at 80 degrees C and chromatographic separation of the peptides using SE-Sephadex. The Cys16-Cys40 disulfide bridge could be reduced selectively by sodium borohydride with no loss in biological activity. This property and the covalent structure correspond to that of the intracellular inhibitor from bovine organs, which is largely homologous in its amino acid sequence to the secretory inhibitor from the snail. The complete covalent structure of isoinhibitor K will be presented. The snail inhibitor is less stable against proteolytic inactivation by thermolysin and against thermal denaturation at pH 8.0 than the inhibitor from bovine organs (**Kunitz** inhibitor).

L3 ANSWER 16 OF 16 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 76043681 MEDLINE
DOCUMENT NUMBER: 76043681 PubMed ID: 1081050
TITLE: Trypsin-kallikrein isoinhibitor K (type **Kunitz**) from snails (Helix pomatia). Purification and characterization.
AUTHOR: Dietl T; Tschesche H
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1975 Oct 15) 58 (2) 453-60.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197602
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 20000303
Entered Medline: 19760202

AB A basic proteinase inhibitor, isoinhibitor K, was purified by SE-Sephadex C-25 column chromatography from the mixture of acid-stable and heat-stable isoinhibitors of the snail (Helix pomatia). Isoinhibitor K is homogeneous in polyacrylamide gel, cellulose acetate and polyacrylamide-dodecylsulfate electrophoresis. From the electrophoretic mobility in dodecylsulfate-polyacrylamide gel and apparent molecular weight of 6500 +/- 200 was estimated. From the amino acid composition the inhibitor consists of 58 amino acid residues. It contains three disulfide bridges, a C-terminal valine and a lysine residue at the reactive site. Isoinhibitor K inhibits the enzymes: bovine trypsin and chymotrypsin, porcine plasmin and pancreatic kallikrein, the trypsin-like component of Streptomyces griseus proteinase-pronase E, and fungi proteinase K from Tritirachium album Limber, which is only inhibited very slightly in contrast to the effect of the mixture of isoinhibitors. The inhibitory effect of isoinhibitor K against these enzymes is compared to that of the mixture or of other isoinhibitors. The following enzymes are not inhibited by isoinhibitor K: Aspergillus proteinase P and alkaline bacillus proteinase 2231 (Rohm),

which both are inhibited by the mixture of isoinhibitors. Porcine elastase, bacterial proteinase N (M) (Rohm), and a trypsin-like proteinase from wheat are not inhibited, porcine acrosin and porcine serum kallikrein only to a very minor extent by the mixture of isoinhibitors. Reactive-site peptide-bond cleavage during inhibition could not be detected. Thus, the inhibitory behaviour is just as broad in specificity and as unusual as that of the trypsin-kallikrein inhibitor (**Kunitz**) from bovine organs. The N-terminus is blocked by pyroglutamic acid. Isoinhibitor K is the main component of the isoinhibitors secreted into the **mucus** and amounts to 35-40% of the mixture.

L7 ANSWER 1 OF 13 MEDLINE
ACCESSION NUMBER: 1998347595 MEDLINE
DOCUMENT NUMBER: 98347595 PubMed ID: 9682673
TITLE: **Aprotinin** reduces nitric oxide production in vitro and in vivo in a dose-dependent manner.
AUTHOR: Bruda N L; Hurlbert B J; Hill G E
CORPORATE SOURCE: Department of Anesthesiology, University of Nebraska Medical Center, Omaha 68198-4455, USA.
SOURCE: CLINICAL SCIENCE, (1998 May) 94 (5) 505-9.
Journal code: 7905731. ISSN: 0143-5221.
PUB. COUNTRY: ENGLAND: United Kingdom
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 19980817
Entered Medline: 19980803

AB 1. Cardiopulmonary bypass is associated with an increase in nitric oxide concentrations, and plasma levels of tumour necrosis factor and interleukin-1. **Aprotinin**, a serine protease inhibitor, commonly used during cardiopulmonary bypass to reduce blood loss, has been demonstrated to exhibit significant anti-inflammatory effects during and after cardiopulmonary bypass. 2. Airway nitric oxide was measured during cardiopulmonary bypass in 10 controls (Group 1), 10 subjects receiving half-dose **aprotinin** (Group 2) and 10 patients receiving full-dose **aprotinin** (Group 3). In vitro, a murine bronchial epithelial cell line (LA-4) was cultured with cytomix (a combination of tumour necrosis factor, interleukin-1, and (gamma-interferon) with and without **aprotinin** in increasing concentrations. Nitrite concentrations, the stable and measureable end-product of nitric oxide oxidative metabolism, were measured in the culture supernatant by chemiluminescence. 3. Airway nitric oxide concentrations were increased after 50 min cardiopulmonary bypass compared with that measured at 5 min in controls (53 +/- 5 versus 29 +/- 3 ppb, P < 0.05) but not in the **aprotinin**-treated groups (25 +/- 4 versus 14 +/- 5, Group 2; 21 +/- 6 versus 15 +/- 3 ppb, Group 3). 4. In a dose-dependent manner, nitrite levels (means +/- S.E.M.) were significantly reduced by **aprotinin** at 500 and 1000 units/ml when compared with cells cultured in the presence of cytomix alone (P < 0.05). 5. These data demonstrate that **aprotinin**, in a dose-responsive manner, reduces nitric oxide production in vivo and reduces cytokine-induced nitrite production by murine bronchial epithelial cells in vitro. Since increased airway nitric oxide is found in inflammatory lung diseases, like **asthma**, and anti-inflammatory therapy reduces the concentration of airway nitric oxide, these data support the concept that **aprotinin** is anti-inflammatory during cardiopulmonary bypass.

L7 ANSWER 2 OF 13 MEDLINE
ACCESSION NUMBER: 96152541 MEDLINE
DOCUMENT NUMBER: 96152541 PubMed ID: 8573092
TITLE: Inhibition of human pancreatic proteinases by **mucus** proteinase inhibitor, eglin c and **aprotinin**.
AUTHOR: Belorgey D; Dirrig S; Amouric M; Figarella C; Bieth J G
CORPORATE SOURCE: Laboratoire d'Enzymologie, INSERM U392, Universite Louis Pasteur de Strasbourg, France.
SOURCE: BIOCHEMICAL JOURNAL, (1996 Jan 15) 313 (Pt 2) 555-60.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19970203
Entered Medline: 19960301

AB The kinetic investigation of the inhibition of human pancreatic trypsin 1, trypsin 2 and chymotrypsin A by **mucus** proteinase inhibitor, eglin c and **aprotinin** reveals that (i) the first protein is a potent inhibitor of chymotrypsin A (kass. = 1.4 x 10(6) M-1.s-1, Ki = 71 pM) but forms loose complexes with trypsin 1 (Ki = 0.5 microM) and trypsin 2 (Ki = 18 nM), (ii) eglin c does not inhibit the two trypsins but forms a tight complex with chymotrypsin A (kass. = 3.3 x 10(6) M-1.s-1, Ki < 0.1 nM) and (iii) **aprotinin** is a potent inhibitor of trypsin 1 (kass. = 1 x 10(6) M-1.s-1, Ki < 0.2 nM) and trypsin 2 (kass. = 2.4 x

10(5) M-1.s-1, Ki < 1 nM) but forms a loose complex with chymotrypsin A (Ki = 0.17 microM). These data, together with those published previously on human pancreatic elastase, suggest that a cocktail of **aprotinin** + eglin c might be a better intensive-care drug for acute pancreatitis than **aprotinin** alone, because it will efficiently inhibit all four human pancreatic proteinases. On the other hand, human gastric juice inactivates **mucus** proteinase inhibitor by pepsin-mediated cleavage. This indicates that the fraction of **mucus** proteinase inhibitor that reaches the stomach following aerosol delivery to **cystic fibrosis** patients does not reach the duodenum in an active form and, therefore, does not aggravate the pancreatic insufficiency of these patients.

L7 ANSWER 3 OF 13 MEDLINE
ACCESSION NUMBER: 95298814 MEDLINE
DOCUMENT NUMBER: 95298814 PubMed ID: 7540042
TITLE: Use of **aprotinin** in pediatric lung transplantation.
AUTHOR: Jaquiss R D; Huddleston C B; Spray T L
CORPORATE SOURCE: Department of Surgery, St. Louis Children's Hospital, Washington University School of Medicine, MO 63110, USA.
SOURCE: JOURNAL OF HEART AND LUNG TRANSPLANTATION, (1995 Mar-Apr) 14 (2) 302-7.
Journal code: 9102703. ISSN: 1053-2498.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950726
Last Updated on STN: 19960129
Entered Medline: 19950714

AB BACKGROUND: **Aprotinin** has been shown to decrease perioperative bleeding in adults undergoing cardiac surgery. We evaluated its efficacy in reducing blood loss in pediatric lung transplantation. METHODS: **Aprotinin** was given to a group of pediatric lung transplant recipients (n = 24) identified as being at high risk for bleeding by virtue of preoperative diagnosis of **cystic fibrosis** or previous cardiothoracic operation (group 1). Comparison was made to a group of pediatric recipients (n = 19) believed to be at low risk for bleeding who did not receive **aprotinin** (group 2). All transplantations were accomplished with the use of cardiopulmonary bypass. RESULTS: No difference in intraoperative blood requirement was identified between groups (18 +/- 3 cc/kg [group 1] versus 30 +/- 8 cc/kg [group 2], p = 0.16). Neither postoperative blood transfusion requirement (12 +/- 5 cc/kg [group 1] versus 16 +/- 6 cc/kg [group 2], p = 0.55) nor chest tube output in the first 24 postoperative hours (43 +/- 9 cc/kg [group 1] versus 53 +/- 13 cc/kg [group 2], p = 0.55) was significantly different between groups. Reexploration for bleeding was required in 8% (2 of 25) in group 1 and 16% (3 of 19) in group 2 (p = 0.64). CONCLUSIONS: **Aprotinin** reduced the amount of perioperative hemorrhage in a group of pediatric patients at high risk for bleeding after lung transplantation. The magnitude of the effect could not be quantified but was sufficient to normalize the transfusion requirement to that of a low risk group of patients.

L7 ANSWER 4 OF 13 MEDLINE
ACCESSION NUMBER: 86102648 MEDLINE
DOCUMENT NUMBER: 86102648 PubMed ID: 2417576
TITLE: Immunological studies on patients who received **aprotinin** therapy.
AUTHOR: Yanagihara Y; Shida T
SOURCE: ARERUGI. JAPANESE JOURNAL OF ALLERGOLOGY, (1985 Sep) 34 (9) 899-904.
Journal code: 0241212. ISSN: 0021-4884.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860214

L7 ANSWER 5 OF 13 MEDLINE
ACCESSION NUMBER: 75205141 MEDLINE
DOCUMENT NUMBER: 75205141 PubMed ID: 1080051
TITLE: [Effect of the protease inhibitor **aprotinin** on

pulmonary function and on the inhibitory activity of **sputum** in patients with chronic obstructive **bronchitis**].
Uber die Wirkung des Proteaseinhibitors **Aprotinin** auf die Lungenfunktion sowie die inhibitorische Aktivatt des Sputums bei Patienten mit chronisch-obstruktiver **Bronchitis**.
AUTHOR: Rasche B; Marcic I; Ulmer W T
SOURCE: ARZNEIMITTEL-FORSCHUNG, (1975 Jan) 25 (1) 110-6.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197509
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19750929

AB It has been investigated whether a substitution of protease inhibitor deficiency is indicated in case of chronic obstructive airway disease. As a therapeutic possibility, apronitin isolated from bovine organs (tyasylol), which in vitro inhibits **sputum** proteases up to 80 per cent was tested. Besides infusion, inhalation was chosen for application by which a protease inhibition could be attained. We observed an inhibition of the course of illness associated with a good tolerance of the preparation. Whether a therapy applying the addition of protease inhibitor is reasonable in the long run in chronic diseases cannot yet be concluded from these investigations.

L7 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:438192 CAPLUS
DOCUMENT NUMBER: 113:38192
TITLE: Influence of the trypsin inhibitors **aprotinin** (trasylol) and TLCK, administered locally by osmotic minipumps, on the gelatinolytic activity of acrosin and the transport of spermatozoa in the female reproductive tract of rabbits
AUTHOR(S): Pakzad, Rahim
CORPORATE SOURCE: Inst. Anat., Med. Univ. Luebeck, Luebeck, Fed. Rep. Ger.
SOURCE: Z. Mikrosk.-Anat. Forsch. (1989), 103(6), 957-66
CODEN: ZMAFA2; ISSN: 0044-3107
DOCUMENT TYPE: Journal
LANGUAGE: German

AB The trypsin inhibitors **aprotinin** (I) and TLCK (II, N-.alpha.-p-tosyl-L-lysine chloromethyl ketone) were administered continuously into the lumen of the cervix uteri of sexually mature rabbits by surgically implanted osmotic minipumps. The does were inseminated 6 days after implantation, then sacrificed 2-6 h after insemination and their reproductive tracts prepd. for the gelatin substrate film test and SEM. At a I pumping rate of 50-100 .mu.g/h neither gelatinolytic activity of acrosin (III) nor sperm transport was visibly inhibited. II, at a pumping rate of 10 .mu.g/h, did not influence the proteolytic activity of III; however it seems, presumably because of its toxicity, to destroy the fine structure of epithelial surfaces in the vagino-cervical region and to impair sperm transport. Thus, III is apparently not inhibited by I and II in vivo and may play no immediate role in sperm transport in the female reproductive tract.

L7 ANSWER 7 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:193489 BIOSIS
DOCUMENT NUMBER: PREV199800193489
TITLE: The value of **aprotinin** and tranexamic acid in the treatment of massive hemoptysis.
AUTHOR(S): Kokturk, O.; Firat, H.; Ekim, N.; Akcay, S.
CORPORATE SOURCE: Dep. Chest Dis., Gazi Univ. Sch. Med., Ankara Turkey
SOURCE: European Respiratory Journal Supplement, (Sept., 1997) Vol. 10, No. 25, pp. 413S.
Meeting Info.: Annual Congress of the European Respiratory Society Berlin, Germany September 20-24, 1997 European Respiratory Society
. ISSN: 0904-1850.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 8 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:51910 BIOSIS
DOCUMENT NUMBER: PREV199799351113

TITLE: **Aprotinin** reduces nitric oxide production in vitro and vivo in a dose dependent manner.
AUTHOR(S): Bruda, N. L.; Hurlbert, B. J.; Hill, G. E.
CORPORATE SOURCE: Anesth. Dep., Univ. Nebraska Medical Center, Omaha, NE 68118-4455 USA
SOURCE: Anesthesiology (Hagerstown), (1996) Vol. 85, No. 3A, pp. A130.
Meeting Info.: Annual Meeting of the American Society of Anesthesiologists New Orleans, Louisiana, USA October 19-23, 1996
ISSN: 0003-3022.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L7 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:51909 BIOSIS
DOCUMENT NUMBER: PREV199799351112
TITLE: Mechanism of **aprotinin**-induced reduction of airway nitric oxide during CPB.
AUTHOR(S): Buchele, S.; Roberts, T.; Newland, M.; Hill, G. E.
CORPORATE SOURCE: Anesthesia Dep., Univ. Nebraska Medical Center, Omaha, NE 68198-4455 USA
SOURCE: Anesthesiology (Hagerstown), (1996) Vol. 85, No. 3A, pp. A129.
Meeting Info.: Annual Meeting of the American Society of Anesthesiologists New Orleans, Louisiana, USA October 19-23, 1996
ISSN: 0003-3022.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L7 ANSWER 10 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94372124 EMBASE
DOCUMENT NUMBER: 1994372124
TITLE: Reviews of **aprotinin** and salmeterol xinafoate.
AUTHOR: Levien T.L.; Baker D.E.
CORPORATE SOURCE: Drug Information Center, College of Pharmacy, Washington State University, West 601 First Ave.,Spokane, WA 99204-0399, United States
SOURCE: Hospital Pharmacy, (1994) 29/9 (864-866+868-870+873-874+876-878).
ISSN: 0018-5787 CODEN: HOPHAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L7 ANSWER 11 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93203899 EMBASE
DOCUMENT NUMBER: 1993203899
TITLE: Use of **aprotinin** in lung transplantation.
AUTHOR: Cooper J.D.
CORPORATE SOURCE: One Barnes Hospital Plaza, Queeny Tower,St Louis, MO 63110, United States
SOURCE: Perfusion, (1993) 8/SUPPL. (43-46).
ISSN: 0267-6591 CODEN: PERFER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 009 Surgery
015 Chest Diseases, Thoracic Surgery and Tuberculosis
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although the use of **aprotinin** has been well documented for cardiac surgical procedures, its use in lung transplantation has received less attention. Herein is the experience at Washington University with **aprotinin** in patients undergoing lung transplantation (most with **cystic fibrosis**). In these patients, bleeding from the chest wall is a major problem due to the dense adhesions from chronic infection. **Aprotinin** has a dramatic effect in reducing bleeding.

L7 ANSWER 12 OF 13 WPIDS (C) 2002 THOMSON DERWENT

09/816,860 SEARCH RESULTS/HISTORY

ACCESSION NUMBER: 1996-321851 [32] WPIDS
CROSS REFERENCE: 1990-115996 [15]; 1992-150877 [18]; 1992-331666 [40]; 1992-331723 [40]; 1992-331725 [40]
DOC. NO. CPI: C1996-102546
TITLE: New engineered inhibitors of human neutrophil elastase - contg. **aprotinin**-like Kunitz domain for treating, e.g. **cystic fibrosis** or other respiratory disorders.
DERWENT CLASS: B04 D16
INVENTOR(S): GUTERMAN, S; KENT, R; LADNER, R C; LEY, A C; MARKLAND, W; ROBERTS, B; GUTERMAN, S K; KENT, R B; ROBERTS, B L
PATENT ASSIGNEE(S): (DYAX-N) DYAX CORP; (PROT-N) PROTEIN ENG CORP
COUNTRY COUNT: 20
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9620278	A2	19960704	(199632)*	EN	106
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					
US 5663143	A	19970902	(199741)		147
EP 797666	A1	19971001	(199744)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
JP 10510996	W	19981027	(199902)		116

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9620278	A2		WO 1995-US16349	19951215
US 5663143	A	CIP of	US 1988-240160	19880902
		CIP of	US 1990-487063	19900302
		Div ex	US 1991-664989	19910301
		CIP of	US 1993-9319	19930126
		CIP of	US 1993-133031	19931013
			US 1994-358160	19941216
EP 797666	A1		EP 1995-943819	19951215
			WO 1995-US16349	19951215
JP 10510996	W		WO 1995-US16349	19951215
			JP 1996-520491	19951215

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5663143	A	Div ex	US 5223409
		CIP of	US 5403484
EP 797666	A1	Based on	WO 9620278
JP 10510996	W	Based on	WO 9620278

PRIORITY APPLN. INFO: US 1994-358160 19941216; US 1988-240160 19880902; US 1990-487063 19900302; US 1991-664989 19910301; US 1993-9319 19930126; US 1993-133031 19931013

AN 1996-321851 [32] WPIDS
CR 1990-115996 [15]; 1992-150877 [18]; 1992-331666 [40]; 1992-331723 [40]; 1992-331725 [40]
AB WO 9620278 A UPAB: 19971013
Non-natural protein (I) comprises an engineered **aprotinin**-like Kunitz domain and inhibits human neutrophil elastase (hNE) with Ki < 50 pM. The domain has an amino acid (aa) sequence at least substantially homologous, over a region extending from first to last Cys, with one of the reference sequences EPI-HNE-3 or -4; DPI.1.1, 1.2, 1.3, 2.1, 2.2, 2.3, 3.1, 3.2, 3.3, 4.1, 4.2, 4.3, 5.1,5.2, 5.3, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 7.1, 7.2, 7.3, 7.4, 7.5, 8.1, 8.2, 8.3, 9.1, 9.2 or 9.3, but is not identical to any domain selected from EpiNE- alpha , EpiNE1-8, ITI-E7, BITI-E7-1222 , BITI-E7-141, AMINO 1 or 2, MUTP1, MUTT26A, MUTQE or MUT1619. Also new are (1) DNA (II) encoding (I); (2) expression vectors contg. (I) operably linked to regulatory sequences; (3) transformed cells contg. such vectors. The specification includes the sequences of the reference domains.

USE - (I) are inhibitors of hNE so are used to treat hereditary deficiency of circulating alpha -1-protease inhibitor (API), smoker's emphysema, destruction of lung tissue caused by excessive hNE activity, **cystic fibrosis** and other respiratory diseases.

ADVANTAGE - Unlike API, (I) are small, stable and non-toxic inhibitors of hNE.

Dwg.0/0

09/816,860 SEARCH RESULTS/HISTORY

ABEQ US 5663143 A UPAB: 19971013
A protein that binds and inhibits human neutrophil elastase with a Ki less than about 10 picomolar comprising an amino acid sequence picked from the set of sequences EpiNE1, EpiNE2, EpiNE3, EpiNE4, EpiNE5, EpiNE6, EpiNE7, EpiNE8, EPI-HNE-2, EPI-HNE-3, EPI-HNE-4, BITI-E7, BITI-E7-141, BITI-E7-1222, MUT1619, MUTP1, AMINO1, AMINO2, MUTQE, MUTT26A, EpiNE7.6, EpiNE7.8, EpiNE7.9, EpiNE7.31, EpiNE 7.11, EpiNE7.7, EpiNE7.4, EpiNE7.14, EpiNE7.5, EpiNE7.10, EpiNE7.20, EpiNE7.1, EpiNE7.16, EpiNE7.19, EpiNE7.12, EpiNE7.17, EpiNE7.21, EpiNE7.22, EpiNE7.23, EpiNE7.24, EpiNE7.25, EpiNE7.26, EpiNE7.27, EpiNE7.28, EpiNE7.29, EpiNE7.30, EpiNE7.32, EpiNE7.33, EpiNE7.36, EpiNE7.37, EpiNE7.38, EpiNE7.39, and EpiNE7.40.
Dwg.0/0

L7 ANSWER 13 OF 13 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1994-260420 [32] WPIDS
DOC. NO. CPI: C1994-119037
TITLE: Drug for treating mite allergy e.g. **asthma**, allergic rhinitis and atopic dermatitis - contains **aprotinin**, potato protease inhibitor, soybean trypsin inhibitor, antipine, leupeptin, guanidine fatty acid derivs. guanidino-benzoic acid derivs. and/or amino-di phenol(s).
DERWENT CLASS: B05
PATENT ASSIGNEE(S): (INAD-I) INADA Y; (ONOY) ONO PHARM CO LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 06192085	A	19940712	(199432)*		12

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 06192085	A	JP 1993-234199	19930826

PRIORITY APPLN. INFO: JP 1992-253437 19920831
AN 1994-260420 [32] WPIDS
AB JP 06192085 A UPAB: 19940928
Drug for mite allergy contains **aprotinin**, potato protease inhibitor, soybean trypsin inhibitor, antipine, leupeptin, guanidine fatty acid derivs., guanidinobenzoic acid derivs. and/or aminodiphenols.
Pref. guanidine fatty acids are 6-guanidinohexanoic acid p-ethoxycarbonylphenylester and its acid addn. salts.; guanidinobenzoic acids are p-(p-guanidinobenzoyloxy)-phenylacetic acid N,N-dimethylcarbamoyl methylester, p-guadinobenzoic acid 1-(N, N-dimethylcarbamoyl methoxy-carbonyl) -2-naphthylester, p-guanidinobenzoic acid p-(N-phenyl-N- ethoxycarbonylmethyl carbamoylmethyl) phenylester, etc.; amidinophenol derivs. are 5-(p-(p-amidino phenoxycarbonyl) -benzylidene) -3-ethoxycarbonyl methyl rhodanine, 1-(p-(p-amidinophenoxy carbonyl)benzyl) -2-isopropylimidazole etc.
USE/ADVANTAGE - The drug is used for prevention and treatment of mite allergic diseases such as **asthma**, allergic rhinitis and atopic dermatitis.
Dwg.0/1